AMENDMENT

EXHIBIT A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Title :	HIGH-YIELD METHOD FOR THE PRODUCTION OF HUMAN ANTIBODIES
Appl. No :	10/527,975
Applicant :	Helene Le Buanec
Filed :	March 15, 2005
TC/A.U.	1647
Examiner :	WOODWARD, CHERIE MICHELE
Docket No :	**To be Fulfilled**
Customer No :	**To be fulfilled**
Confirmation No :	7511

DECLARATION OF DANIEL ZAGURY UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-01 450

I, Daniel ZAGURY, declare and states as follows:

1. I am a co-inventor of the above-indentified Application – Serial No. 10/527,975 ("the '975 Application"). I am presently Chairman of the Research and Development Department at the Neovacs Company, which is the assignee of the above-identified Application. My educational and professional experience is presented in the curriculum vitae attached hereto as Exhibit A, which includes a list of the scientific publications wherein I am named as an author or co-author (Exhibit A).

2. As a named co-inventor in the '975 Application, I am familiar with the subject matter that is described and claimed therein. I understand that the pending set of claims contains claims numbered 1-3, and 11-28 and that only claims 1-3 and 21-25 are presently being considered by the examiner.

3. I also understand that claim 1 relates to a "*stable immunogenic product for inducing antibodies raised against a TNFα protein in a subject, characterized in that it comprises protein immunogenic heterocomplexes consisting of associations between (i) TNFα protein molecules and (ii) KLH carrier protein molecules and that more than 1% and less than 40% of the antigenic proteins (i) are covalently linked to carrier protein molecules (ii), and wherein the covalent bonds between one or more TNFα proteins and the KLH protein molecule are made through a bifunctional bond chemical agent consisting of glutaraldehyde*".

4. I have studied and I am familiar with the Final Office action dated of June 23, 2008. I understand that the Examiner has rejected the present invention as being already disclosed by the United States Patent Application published as US 2004/0028647 which names me as the lead inventor and is entitled "Vaccines against cytokines and growth factors derived from malignant tumours" (hereinafter referred to as "Zagury").

5. I understand that according to the Examiner, Zagury describes the stable immunogenic product which is the subject matter of claim 1 of the '975 Application, which immunogenic product, among other features, (i) comprises associations between TNFα protein molecules and KLH carrier protein molecules and (ii) those associations that are formed partly (1%-40%) through covalent links and the remaining ones through non-covalent links.

6. I respectfully submit that the examiner has misunderstood the content of Zagury..

7. First, in contrast to the examiner's statements, there is no disclosure in Zagury of an immunogenic compound comprising both TNFα protein molecules and KLH carrier protein molecules.

8. The examples of Zagury relate to the following vaccines, respectively :

- a vaccine based on the VEGF immunogen, wherein a VEGF aqueous solution is combined with ISA 51 to form an oil emulsion (Example 1),
- a vaccine based on a plasmid containing a sequence encoding IL-10 in a PBS buffer (Example 2),
- a vaccine based on a p53 immunogen that is inserted into a calcium phosphate gel, optionally in the presence of LTμ adjuvant (Preparation 2 and Example 3),
- a vaccine based on a IL-10 immunogen wherein IL-10 and a mutant of the LT toxin are included in PLG microspheres (Example 4),
- a vaccine based on a plasmid containing a sequence encoding IFN-γ plasmid immunogen and LTμ are included in PLG microspheres (Example 5),
- a vaccine based on VEGF immunogen wherein a VEGF stabilized by treatment with glutaraldehyde in an aqueous solution is combined with ISA 51 to form an oil emulsion (Example 6),
- a vaccine based on a conjugate between VEGF and KLH in an aqueous solution, which is combined with ISA 51 to form an oil emulsion (Preparation 10 and Example 7),
- a vaccine based on a conjugate between E7 immunogen from HPV16 and KLH, which is combined with ISA 51 to form an oil emulsion (Preparation 11 and Example 8).

9. Zagury also discloses further immunogenic compounds, none of which involving the use of glutaraldehyde as a coupling reagent, nor any carrier protein (like KLH) for its preparation.

10. It flows from the preceding recitation of the examples of Zagury that the sole conjugate immunogenic compounds prepared by using glutaraldehyde as the coupling reagent that are described therein consist of (i) a VEGF-KLH conjugate, (ii) a E7-KLH conjugate and (iii) a IFNα-KLH conjugate. Thus, Zagury does not actually describe a conjugate between TNFα protein molecules and KLH carrier protein molecules, nor a method for preparing the same.

11. I understand that the examiner supports his ground for rejection on several paragraphs of Zagury:

    - TNFα is included in a specific list of immunogens that may be used (See [0050], page 3 of Zagury),
    - conjugation of the immunogen to KLH using a bifunctional coupling reagent (See [0059], page 4 of Zagury), and
    - "*Glutaraldehyde is taught as the preferred bifunctional coupling reagent in an anti-TNFα vaccine conjugate*" (in reference to [0134], page 7 of Zagury).

12. I agree with the Examiner's statement that TNFα is one of the antigens against which an immune response is reported in Zagury. I also agree that coupling of an antigen of interest to KLH is in the ambit of Zagury. The above-cited VEGF-KLH and E7-KLH conjugates are embodiments of such immunogenic compounds that are actually described in Zagury et al

13. However, I strongly disagree with the above-cited examiner's statement relating to the alleged teachings of paragraph [0134] of Zagury (*"Glutaraldehyde is taught as the preferred bifunctional coupling reagent in an anti-TNFα vaccine conjugate"*), for the reasons set forth below.

14. Paragraph [0134] of Zagury pertains to the preparation of a TNFα immunogen comprising (i) a step of treatment of TNFα with formaldehyde, and then (ii) a step of treatment of the product resulting from step (i) with glutaraldehyde, in accordance to the protocol described for the p53 immunogen (*emphasis added*).

15. The protocol described for the p53 immunogen is disclosed on page 6, at paragraphs [108]-[109] of Zagury. Therein, it is clearly specified that:

    - the p53 immunogen was detoxified by treatment with formaldehyde, and subsequently
    - the detoxified antigen is reacted with glutaraldehyde, before blocking the excess aldehyde groups with glycine.

16. I underline that the protocol for preparing the p53 immunogen as described above does not include any step of coupling of the p53 immunogen with KLH. Consequently, paragraph [0134] that is referred to by the examiner cannot and does not disclose the preparation of a TNFα immunogen by coupling to KLH

17. I hereby declare that both as a highly-skilled researcher in the field of vaccines, and as the lead inventor of Zagury, the method of preparation of a TNFα immunogen such as is described in Paragraph [0134] that is referred to by the examiner is not aimed at preparing a conjugate of TNFα with KLH.

18. Furthermore, in the method of preparation of the TNFα immunogen disclosed in Paragraph [0134], glutaraldehyde is not used as an agent for the coupling of TNFα molecules to any other molecules of interest. Instead, in this method, glutaraldehyde is exclusively used as a bridging agent for generating intra- and inter-molecular covalent bonds in the TNFα molecules, with the view to stabilizing the resulting immunogenic product.

19. Moreover, I also underline that the final step of the said method consists of adding glycine with a view to blocking the still unreacted glutaraldehyde functionality in order to ensure that the final immunogenic product that is obtained is chemically inert. Therefore, because the end-product of the process is chemically unreactive, no further step of coupling to KLH is practically still possible, even if such coupling would have been desired, which it is not.

20. With a view to avoiding any further misunderstanding relating to the disclosure of Zagury, I also declare that the conjugates between the antigenic proteins of interest (namely VEGF, E7 or IFNα) and KLH that were actually prepared by Zagury, given the method of preparation that was used, consist of immunogenic products wherein the said antigenic protein and KLH are linked, one to the other, exclusively or quasi-exclusively through covalent bonds. This statement encompasses all the immuno-conjugates disclosed in Zagury, including those prepared by using glutaraldehyde, Sulfo-SIAB or Sulfo-SMCC as the coupling reagent. However, I will make statements hereafter only about the immuno-conjugates prepared by using glutaraldehyde, because these may appear to be the compounds that are the closest to the stable immunogenic product which is claimed in the '975 Application.

21. The method for preparing an immunogen consisting of a conjugate between VEGF and KLH by using glutaraldehyde as the coupling reagent is disclosed on page 9 in paragraphs [0176]-[0180] of Zagury. The said method comprises the following steps :

    - preparing a KLH protein that is activated by glutaraldehyde by reacting the said KLH protein with glutaraldehyde and then eliminating the excess of unreacted glutaraldehyde by dialysis,

    - adding the VEGF protein to the previously prepared glutaraldehyde-activated KLH, so as to generate covalent bonds between (i) the free aldehyde groups present on the glutaraldehyde-activated KLH and (ii) the VEGF molecules, and then

    - blocking the unreacted free aldehyde groups by adding glycine, before

    - *purifying the resulting mixture by size exclusion chromatography, so as to remove the unreacted VEGF and KLH molecules.*

22. I underline that the method for preparing the E7-KLH or IFNα-KLH conjugates by coupling with glutaraldehyde is the same as the above-described method for preparing the VEGF-KLH conjugate (See paragraphs [0181]-[0187], page 9 of Zagury et al.).

23. The above-cited method described by Zagury provides for the production of immunogenic conjugates in which the antigenic protein molecules and the KLH molecules are linked, one to the other, by covalent bonds because :

    - the antigenic protein molecules are reacted exclusively with activated KLH, which means that the sole possibility for the said antigenic protein to be bound within the final immunogenic construct is by chemical reaction with the free aldehyde groups present on the activated KLH, and

- the unbound antigenic protein molecules are separated from the covalent conjugate product during the final step of size exclusion chromatography.

24. I respectfully submit that the method for preparing the stable immunogenic product that is the subject matter of claim 1 of the '975 Application is substantially and meaningfully different than the method for preparing immunogenic conjugates that is disclosed by Zagury. The method for preparing the stable immunogenic product according to the invention of the '975 Application is summarized from page 30, line 15 to page 31, line 12. This method comprises the following steps :
    - incubating the antigenic proteins (e.g. TNFα) and the carrier molecule (e.g. KLH) in the presence of the coupling chemical agent (e.g. glutaraldehyde),
    - purifying the obtained immunogenic product prepared at the previous step.

25. According to the invention, a specific method for preparing the stable immunogenic product with TNFα and KLH which makes use of glutaraldehyde as the coupling reagent in the first step of the method is disclosed in Example 9, at page 38, lines 10-27 of the '975 Application.

26. Specifically, the method of Example 9 also specifies that the product resulting from the reaction between TNFα, KLH and glutaraldehyde as the coupling agent is subjected to further treatment steps, which are, respectively :
    - removing the excess glutaraldehyde, and then
    - treating the resulting product with formaldehyde, before removing the excess formaldehyde to yield the final stable immunogenic product according to the invention.

27. It is my understanding of the method according to the invention that the specific features with which is endowed the final stable immunogenic product are imparted to it by the specific step characteristics of its method of preparation.

28. More precisely, it is my understanding that the specific features of the first reaction step, which consists of a chemically linking of TNFα to KLH by glutaraldehyde treatment, aside from KLH monomers linked to TNFα monomers, also produces TNFα oligomers, KLH oligomers, as well as KLH oligomers that are covalently linked to TNFα oligomers and KLH monomers that are linked to TNFα oligomers, and in which, at least a part, of the TNFα oligomers are bound to the KLH in the stable final product through non-covalent bonds.

29. It is also my understanding of the method for preparing the stable immunogenic product according to the invention that the presence of non-covalently bound TNFα oligomers within the final stable immunogenic product according to the invention is mandatory since the said method does not comprise a final separation step (e.g. size exclusion chromatography separation step) between the various chemical entities, but only a step of dialysis that allows the removal of non-covalently bound TNFα monomeric forms.

30. I respectfully submit that the comparison I have made in paragraphs 9 to 11 above between the method of Zagury et al. and the invention's method, as well as the resulting structural differences in the final products will make clear that the products prepared according to the method of Zagury. and the product prepared according to the invention of the '975 Application <u>are not and cannot be the same</u>.

31. With a view to technically supporting these statements, I have performed comparative assays that are reported in Exhibit B herein.

32. As it is described in detail in Exhibit B, two compounds were prepared:

- an immunogenic conjugate between TNFα and KLH, that was prepared using the method disclosed in paragraphs [0176]-[0180], page 9 of Zagury et al. (See Figure 1 of Exhibit B), except that the final size exclusion chromatography step of Zagury et al. was not performed. This compound and the method for its preparation will be termed as "*non-purified Zagury et al.*" in the instant Declaration, although the final step of purification was omitted, and
- a stable immunogenic compound comprising TNFα and KLH, that has been prepared according to the method disclosed in Example 9, page 98 of the '975 Application (See Figure 2 of Exhibit B).

33. An additional compound has been prepared by performing the method of Zagury that is referred to above and that is disclosed in Figure 1 of Exhibit B, to which an additional step of 48 hours formaldehyde treatment (like for the stable immunogenic product according to this invention) has been introduced. This product will also be termed "*formol non-purified Zagury et al.*" in the instant Declaration.

34. Figure 3 of Exhibit B shows the pattern of a size exclusion chromatography performed on the conjugate compound that was prepared according to "*non-purified Zagury et al.*".

35. In Figure 3 of Exhibit B, it can be seen that the exclusion chromatography of a mixture of native KLH and human TNFα (red curve) separates in two peaks, one for native

KLH (with a retention time ranging from about 45 minutes to about 75 minutes and the highest value at about 58 minutes) and one for TNFα (with a retention time ranging from about 75 to about 90 minutes and the highest value at about 84 minutes).

36. In Figure 3 of Exhibit B, it can also be seen that the exclusion chromatography of the conjugate compound prepared according to ""*non-purified Zagury et al.*"". (blue curve) yields to :

- a main peak (with a retention time ranging from about 50 minutes to about 70 minutes with the highest value at about 57 minutes) corresponding to the covalent conjugate between TNFα and KLH, and
- a small peak (with a retention time ranging from about 82 minutes to about 86 minutes with the highest value at about 84 minutes) corresponding to free TNFα molecules that have not reacted with the KLH molecules pre-activated with glutaraldehyde.

37. It is herein underlined that the chromatography profile of the conjugate compound prepared according to "*non-purified Zagury et al.*" (blue curve) illustrates that the final step of size exclusion chromatography of the method according to Zagury performs an effective separation between (i) the TNFα-KLH covalent conjugate and (ii) the free TNFα molecules that had not reacted with the KLH molecules previously pretreated with glutaraldehyde.

38. It thus flows from the experimental data shown in Figure 3 of Exhibit B that the conjugate compound prepared according to Zagury, which includes the final step of

size exclusion chromatography, does not contain free TNFα molecules that have not reacted with KLH.

39. I respectfully submit that the results of Figure 3 of Exhibit B clearly demonstrate that, in a conjugate compound prepared according to Zagury, the TNFα molecules are all covalently bound to the KLH molecules.

40. Thus, it results that the TNFα-KLH conjugate compound prepared according to Zagury does not consist of a *stable immunogenic product for inducing antibodies raised against a TNFα protein in a subject, characterized in that it comprises protein immunogenic heterocomplexes consisting of associations between (i) TNFα protein molecules and (ii) KLH carrier protein molecules and that* ***more than 1% and less than 40% of the antigenic proteins (i) are covalently linked to carrier protein molecules*** *(ii), and wherein the covalent bonds between one or more TNFα proteins and the KLH protein molecule are made through a bifunctional bond chemical agent consisting of glutaraldehyde*

41. The sole conclusion resulting from my above remarks is that the stable immunogenic product according to the instant invention is clearly distinct from the conjugate products that are described by Zagury.

42. I also wish to refer to the results depicted in Figure 4 of Exhibit B, which consists of a photograph of a SDS-PAGE electrophoresis pattern that I have performed using the following starting products:

- a mixture of molecular weight markers (lane 1),

- a stable immunogenic product comprising TNFα and KLH (this invention) prepared as described in Figure 1 of Exhibit B, (lane 2),
- a conjugate compound between TNFα and KLH (Zagury et al.) prepared as disclosed in Figure 2 of Exhibit B, ("*non-purified Zagury et al.*")(lane 3),
- a conjugate compound between TNFα and KLH prepared as disclosed in Figure 2 of Exhibit B to which method an additional 48 hours formol treatment step has been introduced (lane 4) ("*formol non-purified Zagury et al.*"),
- free KLH (lane 5), and
- free TNFα (lane 6).

43. It is recalled that the sole difference between (i) the method for preparing the end-product that is specified in Figure 2 of Exhibit B that was subjected to SDS PAGE electrophoresis in lane 3 of Figure 4 (ii) and the product disclosed in the document of Zagury cited by the examiner consists of the omission of the final purification step by exclusion chromatography allowing the removal of the unreacted TNFα monomers ("*non-purified Zagury et al.*").

44. The reason why the final step of size exclusion chromatography was omitted for the products prepared according to "*non-purified Zagury et al.*" is that this final step leads to a strong dilution of the final product which is detrimental to the performance of a SDS PAGE electrophoresis, since the latter technique requires a significant amount of product.

45. The drawback of the omission of the final size exclusion chromatography step for preparing the products according to "*non-purified Zagury et al.*" lies in the fact that the end-products migrated in lane 3 of Figure 3 do no consist exactly of the final products

of the method from Zagury, since unreacted TNFα monomers have not been removed.

46. The positive consequence of such a step omission is that the end-products prepared according to "*non-purified Zagury et al.*" are more "comparable" to the stable immunogenic product according to this invention (lane 2), which method of manufacture does not include any final step of size exclusion chromatography.

47. Yet further, the end-products migrated in lane 4, which has also been subjected to a 18h formol treatment step ("*formol non-purified Zagury et al.*"), like the stable immunogenic product according to this invention, is even more "comparable" to the invention's immunogenic product.

48. It is herein to be reminded that a SDS-PAGE electrophoresis consists of an electrophoresis that is performed in "denaturing conditions", in which the protein conformation is altered and protein molecules assume statistically a linear shape, and wherein non-covalently bound proteins are dissociated in their respective free forms.

49. In Figure 4 of Exhibit B, the protein bands are revealed by using anti-TNFα antibodies. As it can be seen in Figure 4 of Exhibit B, the stable immunogenic product according to the invention (lane 2) comprises a large number of TNFα-containing chemical entities having a wide range of apparent molecular mass values.

50. These TNFα-containing chemical entities comprise monomers of TNFα (at the bottom of the electrophoresis gel) as well as a series of chemical entities having apparent molecular mass values higher than that of TNFα monomers and lower than TNFα-

KLH covalent conjugates, these latter molecules being visible at the top of the gel in lane 2 because they do not migrate at all.

51. My understanding is that these numerous TNFα-containing chemical entities of intermediate apparent molecular mass values consist of a family of TNFα oligomers having distinct chain length.

52. The presence of such a number of TNFα-containing chemical entities that were initially comprised in the stable immunogenic product according to the instant invention means that those entities were not covalently bound, one to the others, nor to KLH, in the said stable immunogenic product, before dissociation, due to the denaturing conditions that were used for performing the SDS-PAGE electrophoresis migration.

53. Conversely, Figure 4 of Exhibit B also shows that the conjugate product prepared according to Zagury. (lane 3 for "*non-purified Zagury et al.*"., and lane 4 for "*formol non-purified Zagury et al.*") comprises an amount of free TNFα monomers, the remaining of the said product consisting of the KLH molecules onto which are covalently bound the TNFα molecules, that are visible at the top of the gel in lanes 3 and 4 because they do not migrate at all.

54. More precisely, the free TNFα monomers are visible as the protein band located at the bottom of each of lanes 3 and 4 (apparent molecular mass of less than 20 kDa). The intermediary protein band located at more than 25 kDa of each of lanes 3 ("*non-purified Zagury et al.*") and 4 (Modified "*formol non-purified Zagury et al.*") are likely to

correspond to dimers or trimers of TNFα (the physiological form of TNFα consists of a homo-trimer complex protein).

55. Finally, the protein bands located approximately between 30 kDa et 50 kDa which are clearly visible in lane 4 ("*formol non-purified Zagury et al.*") are likely to correspond to small TNFα oligomers that result from the bridging of formerly unreacted TNFα monomers during the step of formol treatment (not present in the method according to Zagury) that stabilizes the immuno-conjugate.

56. The free TNFα monomers or small TNFα oligomers that are present in the products in lane 3 ("*non-purified Zagury et al.*") and 4 ("*formol non-purified Zagury et al.*") are then removed by the final step of size exclusion chromatography according to the method disclosed by Zagury. The removal of these low molecular mass protein species by the size exclusion chromatography step is illustrated in Figure 3 which shows a clear separation without any overlap between (i) a TNFα-KLH immunoconjugate according to "*non-purified Zagury et al.*" (or even KLH molecules alone) and (ii) TNFα molecules.

57. The results of Figure 4 of Exhibit B, as far as they concern the conjugate product prepared according to Zagury, confirm the chromatography data that I discussed above in reference to Figure 3.

58. Additionally, I have performed immunization of mice with the conjugate product prepared according to "*non-purified Zagury et al.*". and with the stable immunogenic product according to the invention, respectively.

59. At Day 0, mice were injected intramuscularly with 0.5 µg of the corresponding immunogen, and then receive intramuscularly a booster dose of 0.5 µg at Day 18. Blood punctures were performed at Day 35 and at Day 59, respectively.

60. Then, the anti-TNFα and the anti-KLH antibody titers were measured, both at Day 35 and Day 59.

61. The results are shown in Exhibit B on Figures 5 (anti-TNF, D35), 6 (anti-TNF, D59), 7 (anti-KLH, D35) and 8 (anti-KLH, D59), respectively.

62. The results in Figures 5-8 show that the stable immunogenic product according to the invention of the '975 Patent is endowed with a far higher immunogenicity than the conjugate compound prepared according to "*non-purified Zagury et al.*", as shown in Table 2 below.

Table 2 : Comparative analysis of Immunogenicity (Figures 5 and 6)

	Day of blood puncture	
	Day 35	**Day 59**
Product		
This invention	1,600*(a)	50,000(b)
Zagury et al**.	750	34,000

*anti-TNFα antibody titer

** "*non-purified Zagury et al.*"

: $p = 0.01563$

: $p = 0.0625$

63. The results of Figures 7 and 8 and Table 2, also show that the stable immunogenic product according to the invention exhibits a significantly higher immunogenicity as regards the raising of antibodies directed against KLH.

64. I have also performed assays aiming to determine the neutralizing capacity of the anti-TNFα antibodies raised in the animals immunized with the stable immunogenic product according to the invention and with the conjugate product prepared according to "*non-purified Zagury et al.*", respectively.

65. The results are shown in Figure 9 (antibodies collected at Day 35) and Figure 10 (antibodies collected at Day 59), respectively.

66. The results from figures 9 and 10 are summarized in Table 3 below.

Table 2 : Comparative analysis of the anti-TNFα antibodies neutralizing capacity (Figures 9 and 10)

	Day of blood collection	
	Day 35	**Day 59**
Product		
This invention	2,200*(a)	12,500(b)
Zagury et al.**	650	5,000

*NC_{50} anti-TNFα antibody neutralising capacity

** "*non-purified Zagury et al.*"

: $p = 0.03125$

: $p = 0.03125$

67. The results from Figures 9 and 10 and Table 3 show that the anti-TNFα antibodies that were collected from the mice immunized with the stable immunogenic product according to the invention possess a far higher neutralizing capacity against human TNFα than those collected from the mice immunized with the conjugate product prepared according to "*non-purified Zagury et al.*"

68. The information and data included in this Declaration show that the structural features of the stable immunogenic product according to the invention and those of the conjugate product prepared according to "*non-purified Zagury et al.*" (and thus even more the conjugate product according to Zagury) can be unambiguously distinguished. Therefore, Zagury does not in any way explicitly or inherently disclose the stable immunogenic product claimed in the '975 Application..

69. I wish to also respectfully submit that the results contained in the appended Exhibit B also show that the distinctive structural features of the invention's stable immunogenic product lead to distinctive immunogenic properties, as compared with the conjugate product taught by Zagury. It is shown herein that the invention's stable immunogenic product is far more immunogenic than the product taught by Zagury et al.

70. It is also shown herein that the invention's stable immunogenic product induces the production of anti-TNFα antibodies that are endowed with a far higher anti-TNFα neutralizing capacity, as compared with the antibodies that are induced by immunization with the conjugate product taught by Zagury.

71. The present Declaration includes the appended Annex containing Figure 1 and Figure 2 referred to herein.

72. I declare that all statements made in this declaration of my knowledge are true and that all statements made on information and belief are believed to be true ; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardize the validity of the application or any patent issued thereon.

Signed at Paris France

this 15 day of June, 2009

Daniel ZAGURY

DECLARATION

EXHIBIT A

EXHIBIT A

DANIEL ZAGURY, M.D., PHD.

RESUMES OF SCIENTIFIC LEADERSHIP

Diplomas and National Awards

1950 Doctor of Medicine (Paris, France)

1957 Doctor of Biology (Sorbonne University, Paris, France)

1960 PhD, Sciences (Sorbonne University, Paris, France)

1961 University Lecturer in Sciences (Paris, France)

1965 University Lecturer in Histology-Embryology (Paris Medical School, France)

1965 Awarded title of University Lecturer in Histology-Embryology by the aggregation examination (Paris, France)

1968 Professor, Medical School of Reims (France)

1968 Biologist in charge of hospital service (Paris, France)

1976 Professor, University Pierre et Marie Curie (Paris, France)

Overseas Awards and Hospital Functions

Hospital Doctor, Resident

- 1951-1952 Harlem Hospital (New-York, USA)
- 1952-1953 Harris Hospital (Fort Worth, USA)
- 1962-1965 Professor, Medical School of Algiers and Chairman of Medical Biology
- 1966-1967 Associate Professor of Anatomy (Columbia University, USA)

University and Hospital Functions

Professor, University Pierre et Marie Curie and Chairman of Cell physiology (Paris, France)

Chairman of the Immunology Department of the Cancer Hospital Jean Godinot at Reims (France)

Chairman of the Research and Development Council at Neovacs SA (Paris, France)

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DECLARATION

EXHIBIT B

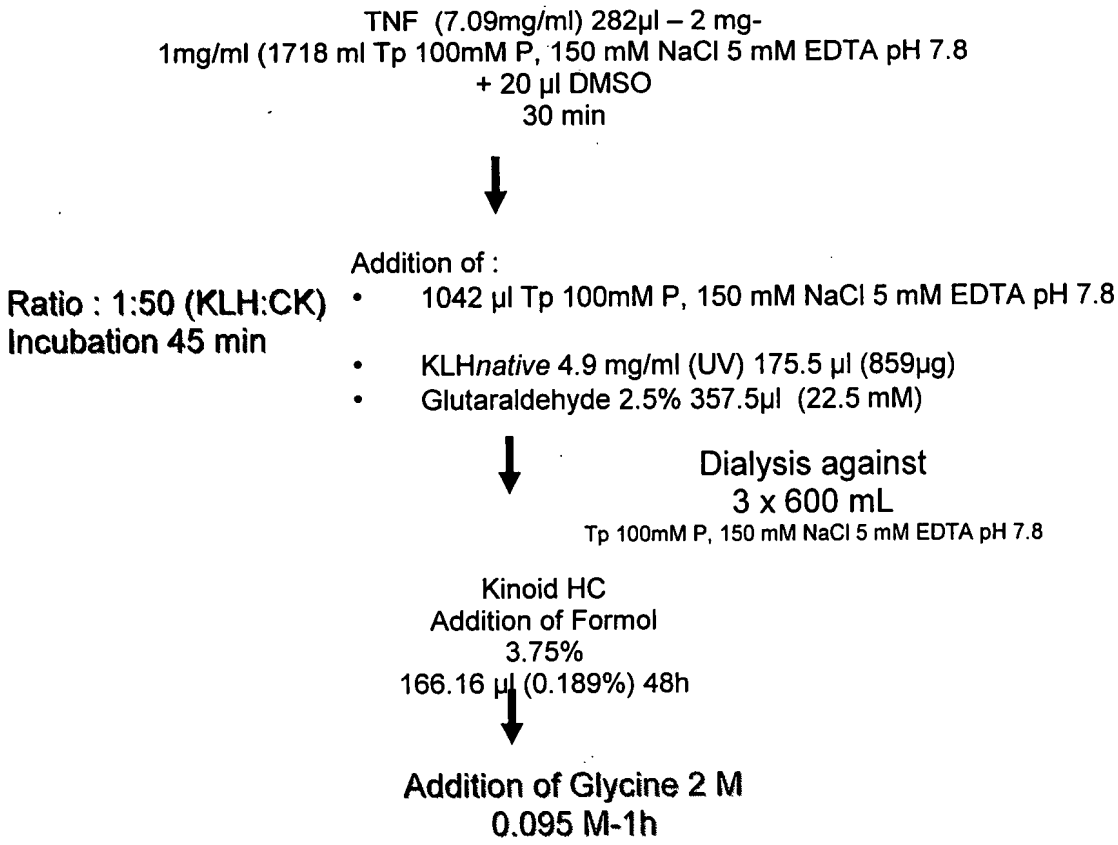


Figure 1 : Method for the preparation of a stable immunogenic product according to Example 9 of US 10/527,975

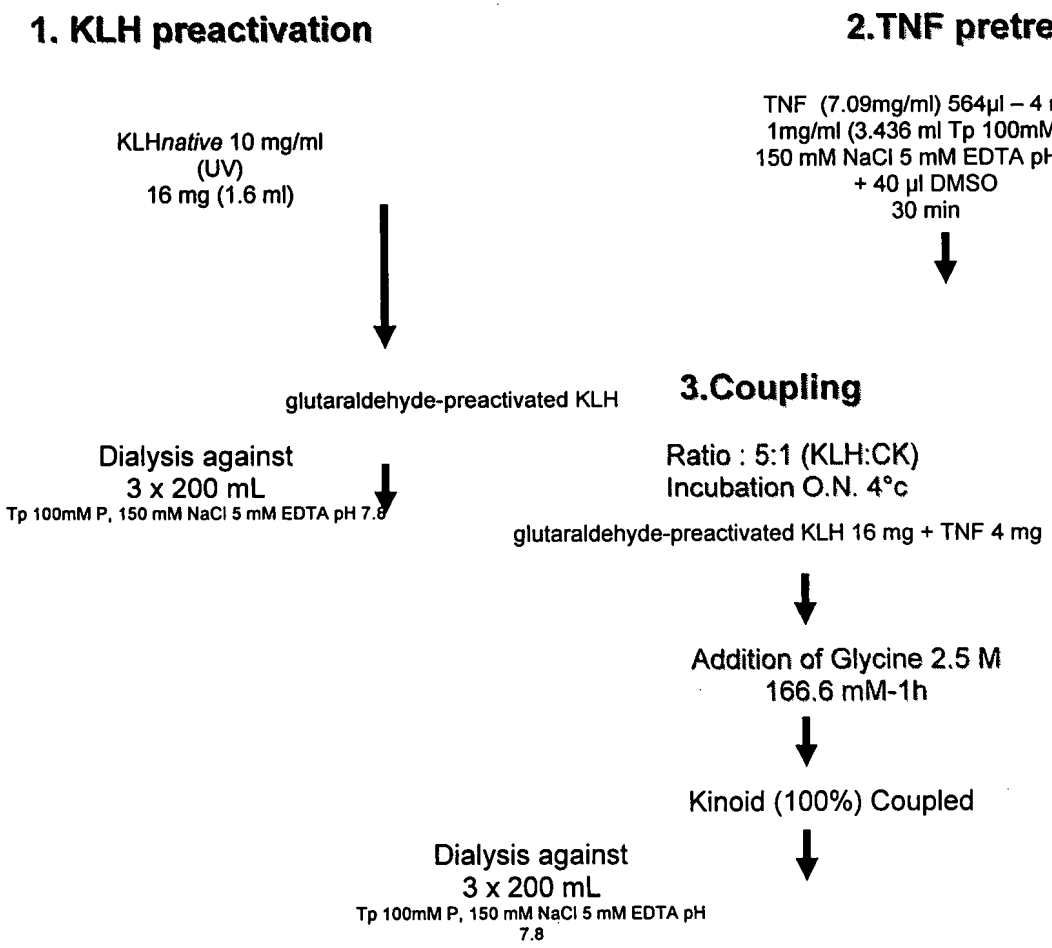


Figure 2 : Method for preparing a TNFα-KLH immuno-conjugate according to Zagury et al.

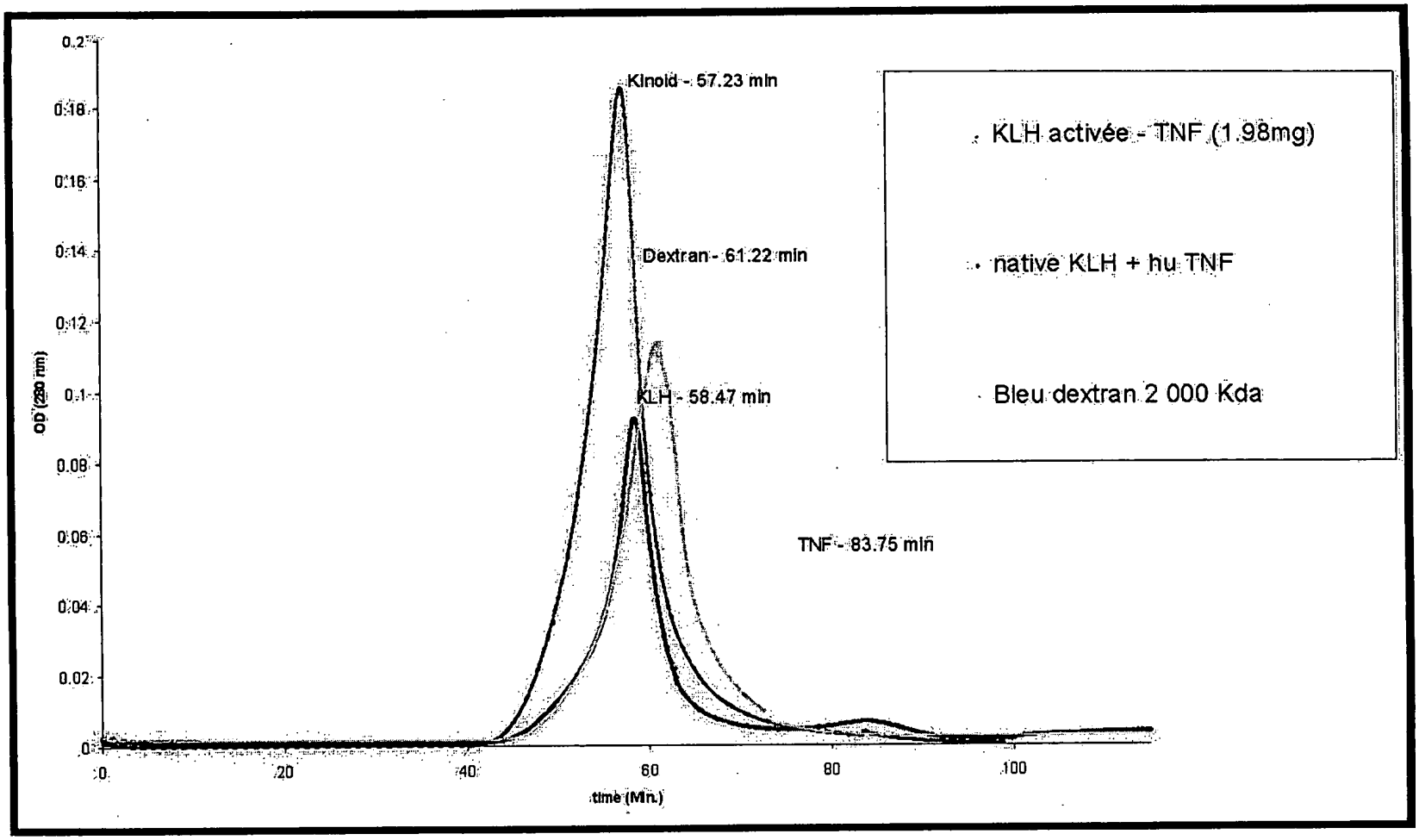
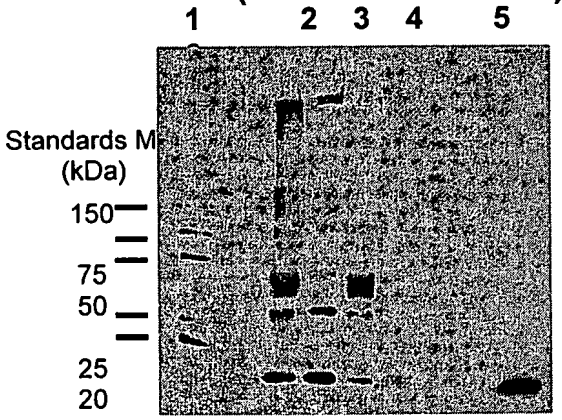


Figure 3 : Size exclusion chromatography profile of (i) Dextran Blue (yellow curve), (ii) a mixture of KLH and of recombinant human TNFα (red curve) and (iii) a TNFα-KLH immuno-conjugate according to Zagury et al.

Western Blot:

- **SDS PAGE (12%),**
- **Détection :**
  - **Polyclonal anti Hu TNF (BAF 210) biotinylé : 50ng/ml**
  - **Streptavidine –HRP (Southern Biotech) 1/6000**



1 : Mw markers (Bio-Rad 161-0363)
2 : Invention's product 2 µg
3 : Zagury et al. without formol treatment 2µg
4 : Zagury et al. (2µg)
5 : KLH (0.5µg)
6 : TNF - Batch 102C (0.5µg)

Figure 4 : SDS PAGE electrophoresis

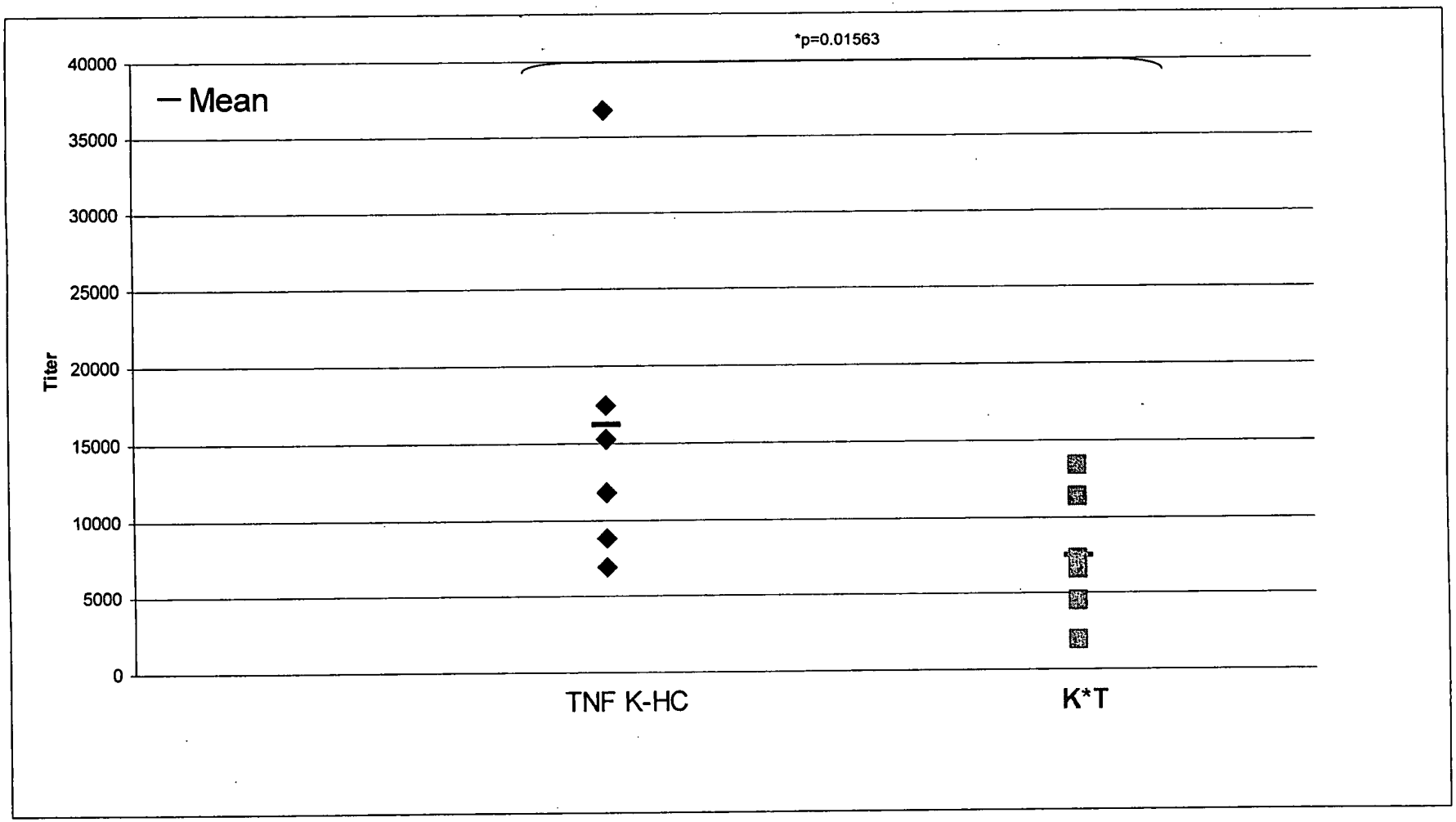


Figure 5 : Day 35 immunogenicity against human TNFα of (i) the stable immunogenic product of this invention ("TNF K-HC") and of the TNFα-KLH imuno-conjugate prepared according to Zagury et al. ("K*T"). Ordinate : anti-TNFα antibody titer.

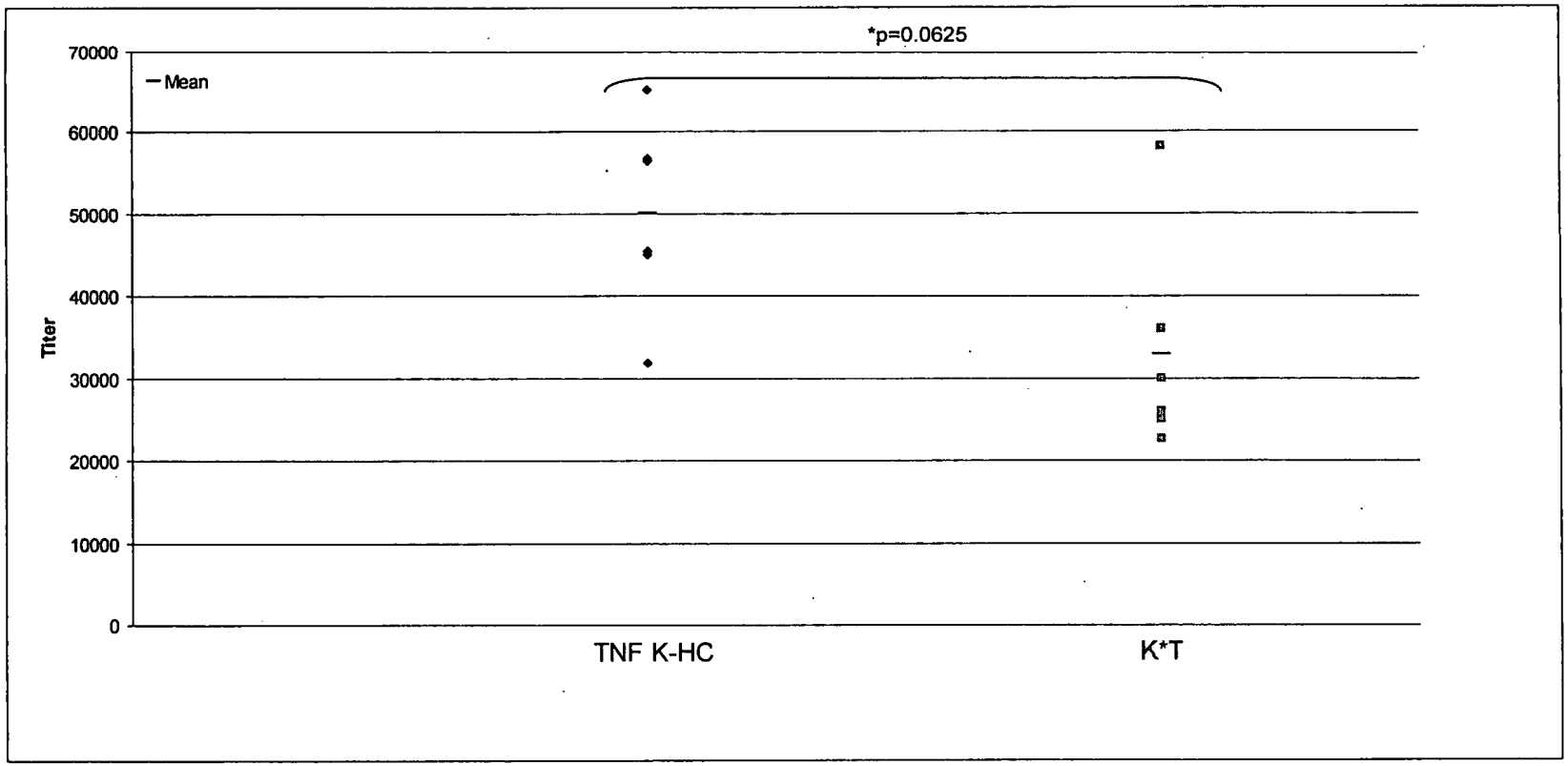


Figure 6 : Day 59 immunogenicity against human TNFα of (i) the stable immunogenic product of this invention ("TNF K-HC") and of the TNFα-KLH imuno-conjugate prepared according to Zagury et al. ("K*T"). Ordinate : anti-TNFα antibody titer.

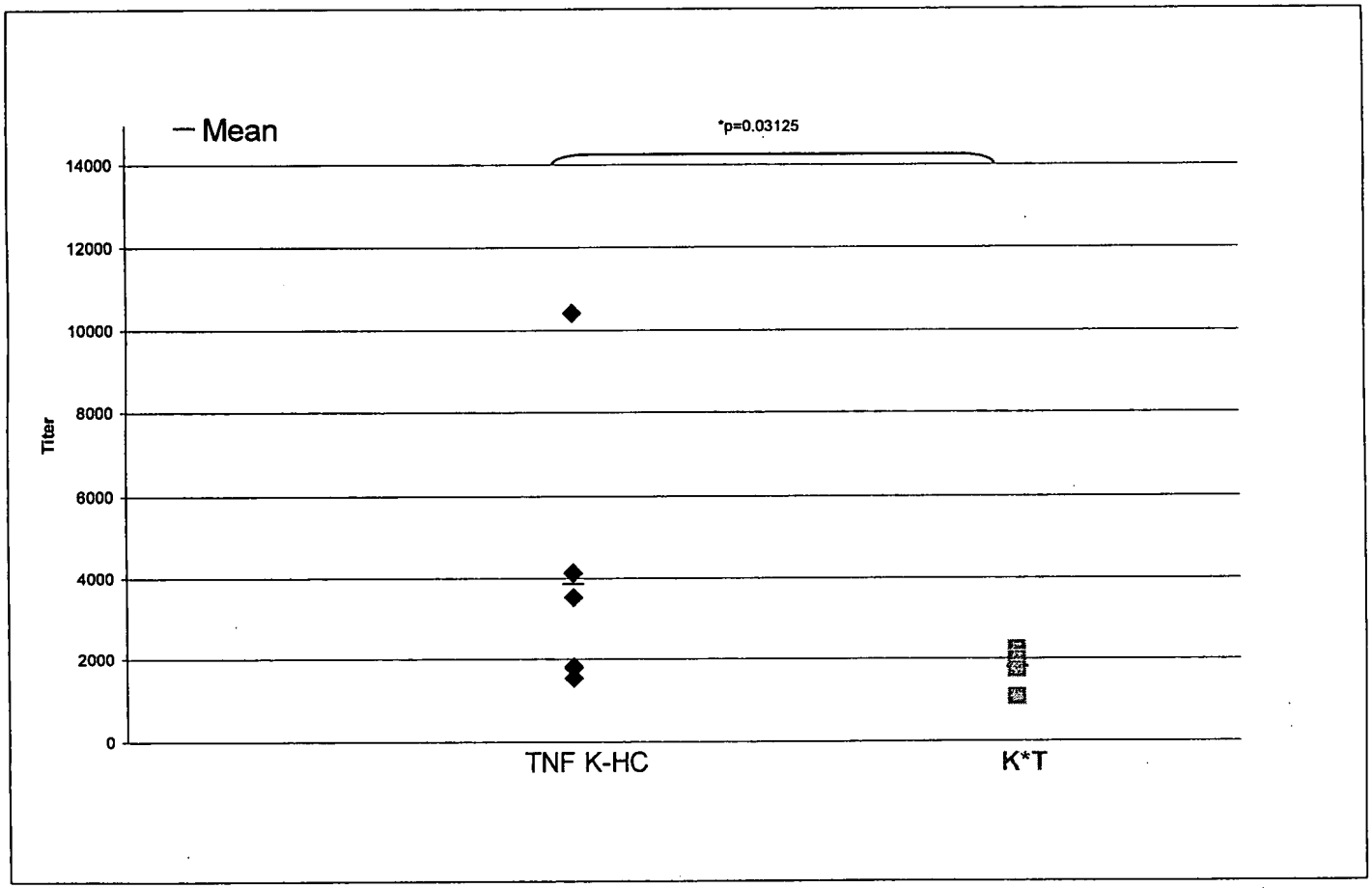


Figure 7 : Day 35 immunogenicity against KLH of (i) the stable immunogenic product of this invention ("TNF K-HC") and of the TNFα-KLH imuno-conjugate prepared according to Zagury et al. ("K*T"). Ordinate : anti-KLH antibody titer.

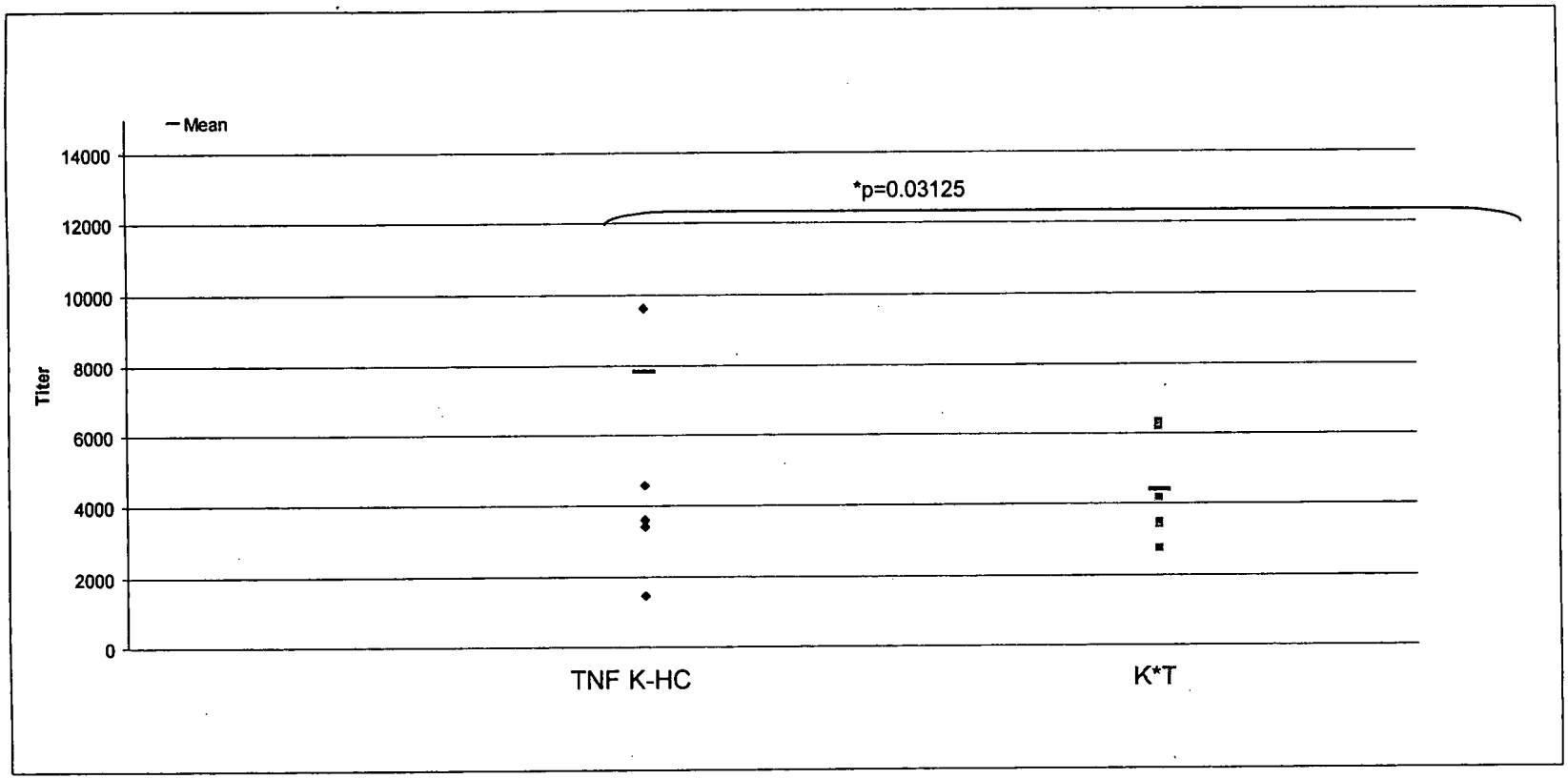


Figure 8 : Day 59 immunogenicity against KLH of (i) the stable immunogenic product of this invention ("TNF K-HC") and of the TNFα-KLH imuno-conjugate prepared according to Zagury et al. ("K*T"). Ordinate : anti-KLH antibody titer.

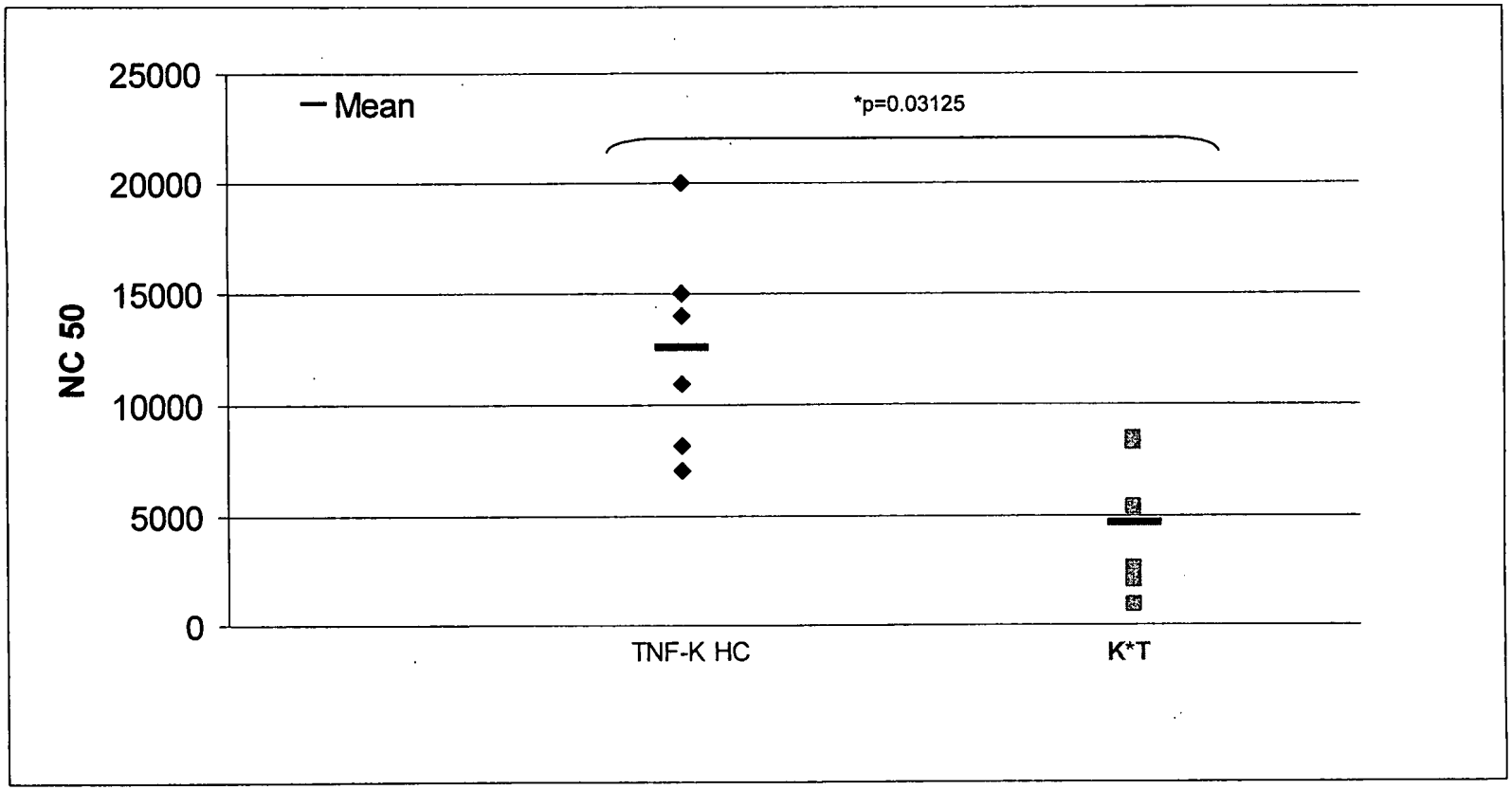


Figure 10 : Neutralizing capacity (NC_{50}) of the antibodies produced at Day 35 after immunization with (i) the stable immunogenic product of this invention ("TNF K-HC") and of the TNFα-KLH imuno-conjugate prepared according to Zagury et al. ("K*T").

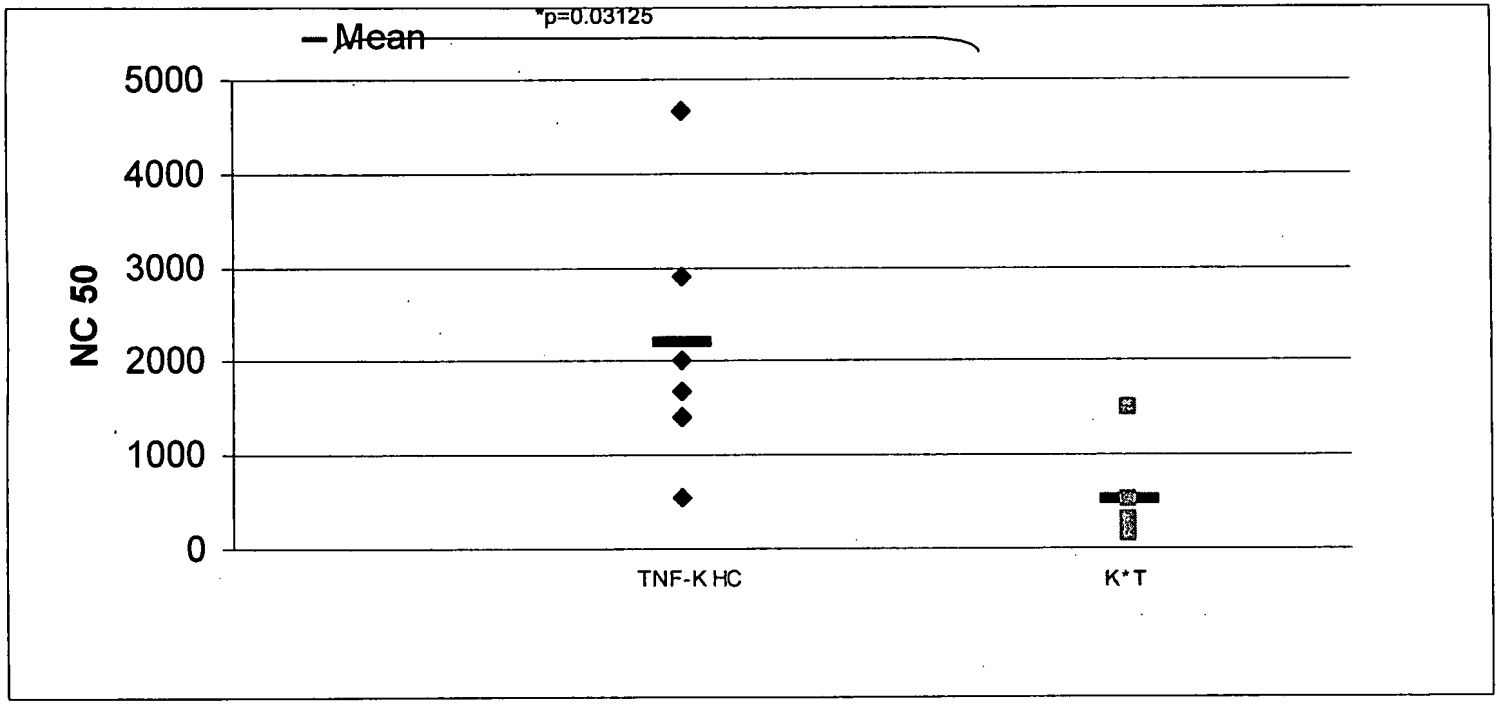


Figure 9 : Neutralizing capacity (NC_{50}) of the antibodies produced at Day 35 after immunization with (i) the stable immunogenic product of this invention ("TNF K-HC") and of the TNFα-KLH imuno-conjugate prepared according to Zagury et al. ("K*T")